VASODILATORS: EVALUATION AND CLINICAL PHARMACOLOGY

Edited by
YOUNG W. CHO
and
ROBERT D. ALLISON

VASODILATORS: EVALUATION AND CLINICAL PHARMACOLOGY

Includes papers presented at the

Louisiana State University
Clinical Pharmacology Symposium
on Evaluation of Peripheral Vasodilators

New Orleans, Louisiana, April 29-30, 1971

Edited by

YOUNG W. CHO, M.D.
Louisiana State University Medical Center
New Orleans, Louisiana

and

ROBERT D. ALLISON, PH.D.
Scott and White Clinic
Temple, Texas

INSTRUMENT SOCIETY OF AMERICA
Pittsburgh

Library of Congress Catalog Card Number 73-83401
ISBN 87664-214-8

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FOREWORD

This monograph is the result of a meeting of a large group of interested physiologists, pharmacologists, chemists and clinicians who were assembled for the purpose of critically analyzing the methods used and the results obtained from studies of drugs with actions on the peripheral circulation. The experts were chosen for their expertise in certain methodologies and their special knowledge about certain drugs. The group was assembled to discuss, in open forum, the advantages and pitfalls of certain methods, their sensitivity, and specificity, as well as to determine the best methods for demonstrating the efficacy of peripheral vasodilators. The anatomic areas included in the studies were primarily those of the peripheral blood vessels including those of the limbs and certain organs such as the head. The circulation to the heart and coronary arteries was excluded from the discussion. Some of the methods discussed included clearance techniques with various isotopes, blood flow studies using plethysmographic methods and Doppler velocity methods; blood pressure techniques; thermography and skin temperature measurements. Finally, a survey by all experts was made to determine important guidelines and significant elements that should be included in studies on the peripheral circulation. This portion of the conference was of particular value to those planning protocols for future studies. It is believed that this volume represents the current state of our understanding of the methods by which peripheral circulatory vasodilators may be studied and therefore is a contribution to students and investigators. It is apparent that much is yet to be learned and new methods to be developed in this field.

Travis Winsor, M. D.

Preface

Young W. Cho, M. D., Ph. D.
Robert D. Allison, Ph. D.

In the spring of 1971 approximately 40 medical investigators, primarily interested in the problems of "peripheral vasodilators" and peripheral vascular disorders, joined a dozen or so medical scientists from the pharmaceutical industries to discuss the ways and means of evaluating peripheral vasodilators. This monogram is a compilation of the papers presented at that meeting: Louisiana State University Clinical Pharmacology Symposium: Evaluation of Peripheral Vasodilators (April 29-30, 1971, New Orleans).

Initially, we were hoping to answer many questions raised by the medical societies and practitioners concerning the clinical efficacy of peripheral vasodilators. What is an effective vasodilator? How do we measure or assess the efficacy of vasodilators in patients? What type of patients and how do we select the patient group for treatment with any specific vasodilator? Many other pertinent questions were raised, and were not fully answered from the Symposium. Therefore, we have organized a new society to tackle these problems and named the society "Task Force for the Evaluation of Peripheral Vasoactive Agents" which convened on April 29, 1971, at the L. S. U. Medical Center in New Orleans. Dr. Eugene Strandness was the general chairman of the 1971-72 Symposium and Dr. Travis Winsor was elected general chairman for 1972-73.

Incidently, our new Task Force is formed to supplement the efforts in similar areas of medical science currently conducted by such societies as the International College of Angiology, the Biomedical Division of the Instrument Society of America, American College of Angiology, American Heart Association, American College of Chest Physicians, American College of Cardiology and so on. Most of the members of our Task Force are currently active members of these societies as well and shall work toward the same goals.

We would like to acknowledge the advice given by members of the Departments of Pharmacology, headed by Dr. Thomas Hernandez, and members of the Department of Medicine, headed by Dr. Fred Allison, Jr. Also, many thanks to Mrs. Bea Abene who acted as receptionist during our symposium and who has worked many hours in the preparation of this monogram. The symposium was supported through the staff and facilities of Louisiana State Medical Center in New Orleans. Also our thanks go to Mr. Glenn F. Harvey, Director of Publications and Educations Services of the Instrument Society of America who has been res-

ponsible for the publication of this monograph.

In particular we owe a debt of gratitude to the Pharmceutical Firms and Representatives who provided the funds for this important meeting:

Ives Laboratories - Dr. Clarence Denton
Mead Johnson Research - Dr. Robert Henderson
Marion Laboratories - Dr. Gerald Beckloff
William S. Merrill Co. - Dr. Gunther Frey
Pfizer Medical Research Laboratories - Dr. Clinton Taylor
Smith Kline and French Laboratories - Director of Clinical Research

A special seafood cuisine dinner was sponsored by U S V Pharmaceutical Company and several essential details were made possible through the George M. Anderson special fund.

L.S.U. CLINICAL PHARMACOLOGY SYMPOSIUM

EVALUATION OF PERIPHERAL VASODILATORS

Date: 9:00 A.M. - 5:00 P.M.

April 29 (Thursday) and April 30 (Friday)

MEETING PLACE:

ROOM 503 A and B (FIFTH FLOOR)
LOUISIANA STATE UNIVERISTY MEDICAL CENTER
1542 TULANE AVENUE
NEW ORLEANS, LOUISIANA 70112

GENERAL SYMPOSIUM CHAIRMAN:

DONALD EUGENE STRANDNESS, M.D.
PROFESSOR OF SURGERY
UNIVERISTY OF WASHINGTON SCHOOL OF MEDICINE
SEATTLE, WASHINGTON

GENERAL COORDINATORS:

YOUNG W. CHO, M.D.
ASSOCIATE PROFESSOR
DEPARTMENT OF PHARMACOLOGY
DEPARTMENT OF MEDICINE
LOUISIANA STATE UNIVERSITY MEDICAL CENTER
NEW ORLEANS, LOUISIANA 70112

ROBERT D. ALLISON, Ph.D.
CHIEF, CARDIOVASCULAR PHYSIOLOGY
SCOTT AND WHITE CLINIC
TEMPLE, TEXAS 76501

GENERAL PROGRAMS:

EVALUATION OF PERIPHERAL VASODILATORS

Thursday: April 29, 1971

9:00 A.M. - 9:05 A.M.: Welcome and Introduction
Young W. Cho, M.D.

9:10 A.M. - 12 Noon Session I

Chairman: Eugene Strandness, M.D.

1. 9:05 A.M. Measurement in Medicine.....
E. Attinger, M.D.

2. 9:30 A.M. Pharmacology of Peripheral Circulation...
John E. Maines, Ph.D.

3. 9:50 A.M. Skin Temperature Measurements.....
G. Roth, Ph.D.

4. 10:15 A.M. Thermography and Plethysmography.....
T. Winsor, M.D.

5. 10:35 A.M. Doppler Flowmeter.....
Eugene Strandness, M.D.

6. 11:00 A.M. Impedance Plethysmography.....
Robert D. Allison, Ph.D.

7. 11.25 A.M. Discussion.....
Eugene Strandness, M.D.

LUNCH (12 Noon to 1:00 P.M.)

1:00 P.M. - 4:00 P.M.: Session II

Chairman: Leslie Morris, M.D.

1. 1:00 P.M. Xenon Clearance.....
John Roth, M.D.

2. 1:25 P.M. Microspheres and Hydrogen Clearance.....
John Delaney, M.D.

3. 1:50 P.M. Cerebral Circulation.....
John Seipel, M.D.

4. 2:15 P.M. Intermittent Claudication.....
Richard Lennihan, M.D.

5. 2:40 P.M. Lipoprotein-Abnormalities and Susceptibility to Atherosclerosis.....
Gerald Berenson, M.D.

COFFEE BREAK (3:05 P.M. - 3:15 P.M.)

6. 3:15 P.M. Hepato-renal Circulation.....
Ronald L. Williams, Ph.D.

7. 3:35 P.M. Discussion.....
Leslie Morris, M.D.

THURSDAY EVENING FUNCTIONS: (Will be announced)

Friday: April 30, 1971

9:00 A.M. - 10:00 A.M.: Venous Dynamics

Chairman: Richard Lennihan, M.D.

1. 9:00 A.M. Subhas Mullick, M.D.

2. 9:25 A.M. Ronald Folse, M.D.

3. 9:50 A.M. Discussion

10:00 A.M. - 12 Noon: PANEL DISCUSSIONS

1. 10:00 A.M. - 10:45 A.M.: Moderator:
Harold Karpman, M.D.
Co-Moderator:
Jorge I. Martinez-Lopez, M.D.

What is an effective vasodilator?

Panel Members: Gerald Beckloff, M.D.
Clarence Denton, M.D.
Gunther Frey, M.D.
Robert Henderson, M.D.
William H. Wilkinson, M.D.

2. 10:45 A.M. - 11:30 A.M.: Moderator:
Wesley Moore, M.D.
Co-Moderator:
Simon Markovich, M.D.

What information should be obtained in clinical evaluation of vasodilators?

Panel Members: E. O. Attinger, M. D.
John P. Delaney, M.D.
Ronald Folse, M. D.
James Morrison, M. D.
Travis Winsor, M.D.

3. 11:30 P.M. - 12 Noon: Moderator:
Bok Y. Lee, M.D.
Co-Moderator:
Andre L. Corman, M.D.

What methodology should be included in protocols for evaluating vasodilators?

Panel Members: Richard Lennihan, M.D.
Robert D. Allison, Ph.D.
John Seipel, M.D.
Grace Roth, Ph.D.
Heinz I. Lippman, M.D.

LUNCH (12 Noon - 1:00 P.M.)

1:00 P.M. - 2:30 P.M.: Review of Questionnaire Results
Eugene Strandness, M.D.
Robert D. Allison, Ph.D.

2:30 P.M. - 3:00 P.M.: Closing Remarks and Summary
Travis Winsor, M.D.
Young W. Cho, M.D.

PROGRAM COMMITTEE

Robert D. Allison, Ph.D. - Temple, Texas
Gerald Beckloff, M.D. - Marion Laboratories
Young W. Cho, M.D. - L.S.U. Medical Center
John Delaney, M.D. - Mayo Clinic
Clarence Denton, M.D. - Ives Laboratories
Gunther Frey, M.D. - William S. Merrill Company
Robert Henderson, M.D. - Mead Johnson
Richard Lennihan, M.D. - Wilmington, Delaware
Leslie Morris, M.D. - Pittsburgh, Pennsylvania

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MEASUREMENTS IN CARDIOVASCULAR DISEASE

E.O. ATTINGER, M.D.,PH.D.[1] AND F.M. ATTINGER, PH.D.*[2]

INTRODUCTION

This symposium has been organized as an attempt to establish a general framework within which the clinical efficacy of vasodilators can be quantitatively evaluated. At present, methodology, as well as pertinence and reliability of measurements of vasoactivity, vary widely and clinical results are therefore frequently not comparable between laboratories. Furthermore extrapolations from the relatively simple experimental procedures by which vasoactive substances are generally assessed can be misleading not only because of the methodology employed, but also because of species differences or because of the markedly different behavior and stress responses which characterize individual vascular beds in mammals. Such differences may be even more accentuated in those clinical situations which call for the use of vasodilators. As normal vascular beds, diseased vessels are not operating in isolation, and diagnostic as well as therapeutic decisions must therefore be based on considerations involving not only the cardiovascular system but its interaction with other systems as well. Because of the complexity and variability of the symptomatologies encountered, it would be highly desirable if a generalized patient model were available which could serve as a guide to the interpretation of symptoms, establish their relative weight and predict the relative effectiveness of alternative treatment plans. An approach to such a model, which is based on the most promising strategy for the interpretation and integration of performance indicators in terms of diagnostic and therapeutic decision has been described in detail[1].

The present paper deals primarily with the mechanisms underlying disease processes requiring vasodilator treatment and with the general concepts involved in the assessment of these mechanisms. In medicine, performance criteria for clinical purposes have traditionally been chosen on the basis of convenience (methodology and patient comfort) and of faith. As a result, much of the development in medical instrumentation has been misdirected toward the design of better mousetraps instead of toward new concepts.

*Division of Biomedical Engineering, University of Virginia, Charlottesville, Virginia.
[1]Professor of Biomedical Engineering.
[2]Associate, Division of Biomedical Engineering.

PRESSURE AND FLOW AS INDICATORS OF VASCULAR PERFORMANCE

As far as an evaluation of the direct effects of vasodilators is concerned, a performance analysis of the cardiovascular system of the patient under consideration is clearly required. Such an analysis is based upon the recognition that the primary function of the system, namely transport, is optimized through a hierarchically structured control system. The transport function involves nutrients, work, heat and information. Optimization is aimed at obtaining the best cost-benefit ratio under condition of stress through achieving minimization of transport costs (i.e. the metabolic requirements of the pump as well as of the conducting system) while maximizing the supply to those organs which bear the brunt of the stressload[2].

Within this framework blood flow (Q) and driving pressure (P) become primary performance-indicators. For steady flow in a single tube these two variables are related through the resistance (R):

$$R = \frac{P}{\dot{Q}} \qquad \frac{8\ell n}{\pi r^4} = k/A^2 \tag{1}$$

where ℓ = length of the tube
r = radius of the tube
A = cross sectional area of the tube
n = viscosity of the fluid

The radius, and hence the cross section of a vessel, emerge as the most important determinants of resistance.

For pulsatile flow, which pertains in most segments of the mammalian vasculature, the driving pressure P has to overcome not noly the viscous resistance of the blood and its conduits (as expressed in eq. 1) but also the inertial resistance of the fluid and viscoelastic resistance of the vascular walls. Because of the latter two components, the pressure-flow relationship becomes a frequency dependent Imepdance Z (w)

$$Z(w) = \frac{P(w)}{\dot{Q}(w)} \tag{2}$$

consisting of an axial (Z_{lo}) and a radial (Z_{tr}) component:

$$Z_{lo} = R + jwL - \frac{8n\ell}{\pi r^4} + jw\,\frac{p\ell}{\pi r^2} \tag{3}$$

$$Z_{tr} = \frac{1}{jwC} = \frac{1}{jw}\,\frac{E\,(2a+1)}{3\,r^2\,(a+1)^2} \tag{4}$$

where L = Inertance
w = angular frequency in radians
p = density of blood
E = elastic modulus of vessel wall
a = vessell radius/wall thickness
$j = \sqrt{-1}$

Basically the axial component of the impedance determines how much blood flows through a vascular segment for a given driving pressure, while the radial component accounts for the amount of blood temporarily stored during the cycle because of vascular distensibility. The vessel radius is the most crucial parameter in determining vascular impedance; since resistance depends on its fourth power, inertance on its second power and vascular compliance on its third power[3]. Its value, and hence that of the vascular cross section, are functions of transmural pressure, the physical properties of the vessel wall and of wall thickness. The latter thus presesents the targets at which vasoactive agents are aimed.

In the larger vessels, pulsatile flow can be conceived of as consisting of a central core, where inertial forces dominate and of a peripheral sleeve where viscous forces are the primary determinants. Because these components interact strongly, the expression of impedance becomes rather more complex than the simplified expression given in eq. 3 and 4. The smaller the vessel radius the more important the resistance component of the impedance becomes.

Despite the fact that the total cross section of the vascular bed increased strikingly at the levels of the arterioles, the resistance of these vessels accounts for the major part of the pressure drop in the peripheral circulation. This may at a first glance appear to be paradoxical since in an arrangement of parallel tubes the total resistance R_t is related to the individual resistances R_i by

$$\frac{1}{R_t} = \sum_{o}^{i} \frac{1}{R_i} \qquad (5)$$

A simple numerical example may explain this apparent discrepancy. Assume that five narrow tubes, each of cross sectional area A_n and length ℓ are connected in parallel. Their total cross sectional area thus equals $A_t = 5A_n$. The resistance of a simple tube of cross sectional area $A_w = A_t$ is $R_w = k/A_w^2$ ($A = r^2$), while the resistance of a single narrow tube equals $R_n = k/A_n^2$. The total resistance of the five narrow tubes thus amounts to $R_T = k/5A_n^2$, while the resistance of the single tube is only $R_w = k/A_w^2 = k/25A_n^2$; i.e. the resistance of the five tubes in parallel is five times as

great as that of a single tube of equal total cross sectional area.

Because of the distensibility of vessel walls the pressure flow relationship are nonlinear. For this reason, comparisons of vascular resistance are meaningless, unless they are made under conditions of either similar flow rates or of similar distending pressures. As the transmural pressure rises, the vessel caliber increases and flow resistance decreases as an exponential function of the radius. The physical properties of vessel walls are such, however, that equal pressure increments have progressively less influence on vessel caliber and, therefore, on flow resistance. At high pressures the system behaves more and more as if it were rigid. Changes of this type are characteristic for the aging process. Because of the complexities of the geometry of vascular beds and of the physical properties of their components, equations 1-4 for single, uniform tubes cannot be directly applied to the pressure-flow relationships in entire vascular beds. For this reason an empirical expression has been proposed[4], which relates Flow ($\dot{Q}$) exponentially to Pressure (P)

$$\dot{Q} = cP^n \qquad (6)$$

The exponent n can be interpreted as an indicator of the contractile state of the vasculature. For example, in perfusion experiments of dog hind limbs, flow rates varying from 0.000062 (virtual occlusion) to 8.7 cm^3/min. can be obtained with a perfusion pressure of 10 mmHg and from 1.29 to 125 cm^3/min. with a perfussion pressure of 200 mmHg[5,6]. The curvilinear relationships of eq. 6 is illustrated in fig. 1 for three different levels of the contractile state of the vascular walls[7]. As the latter increases, the curves approach the pressure axis so that for any given level of pressure, flow is less than before. The exponent n can be interpreted as an index of vascular reactivity to changes in perfussion pressure and varies from about 1 to 3. Its value is strongly affected by the tissue metabolism-blood flow ratio. The lowest values for n and the highest values for c are found in the relaxed vascular bed. With maximal dilation induced by a 10-minute period of ischemia and sebsequent perfusion with hypoxic blood the value of n is close to 1.0 for cutaneous beds, and the pressure flow relationships become similar to those which apply to a Newtonian fluid in a system of rigid conduits (eq. 1).

Given a cardiac output the blood flow distribution between the different peripheral vascular beds is a function of the difference between the pressures at the inflow and the outflow